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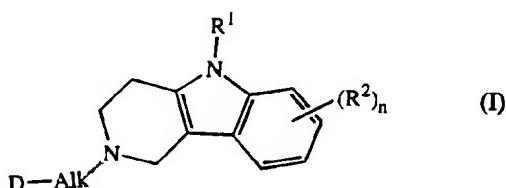
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(54) Tetrahydro gamma-carbolines

(57) The present invention concerns the compounds of formula



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein R¹ is hydrogen, optionally substituted C₁₋₆alkyl, aryl; R² is each independently a halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy or nitro; n is 0, 1, 2 or 3; Alk is C₁₋₆alkanediyl; D is an optionally substituted saturated or unsaturated nitrogen containing heterocycle; and aryl is optionally substituted phenyl; having an affinity for the serotonin receptors. It further relates to their use as a medicine, their preparation as well as compositions containing them.

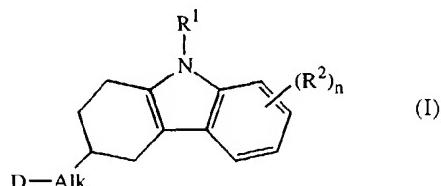
Description

[0001] The present invention concerns tetrahydro γ -carbolines having therapeutic potential in serotonin related disorders. It further relates to their preparation, compositions comprising them and their use as a medicine.

5 [0002] US-4,636,563, published on January 13, 1987, and US-4,672,117, published on June 9, 1987, disclose 2-(heteroaryl-alkyl)-tetrahydro- γ carbolines having antipsychotic activity.

[0003] The compounds of the present invention are novel and have an interesting broad-spectrum receptor-binding profile. In comparison to the structurally related known compounds, they surprisingly exhibit a greater therapeutic breadth.

10 [0004] The present invention concerns the compounds of formula



20 the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

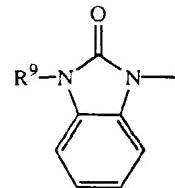
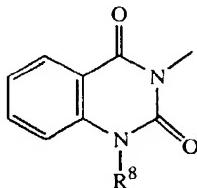
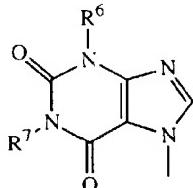
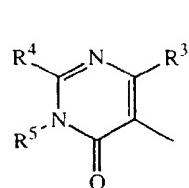
25 R¹ is hydrogen, C₁₋₆alkyl, aryl or C₁₋₆alkyl substituted with aryl;

R² is each independently a halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy or nitro;

n is 0, 1, 2 or 3;

Alk is C₁₋₆ alkanediyl;

D is 1- or 2-benzimidazolyl, 2(3H)benzoxazolone-3-yl or a radical of formula

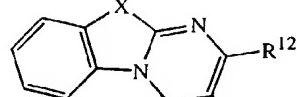
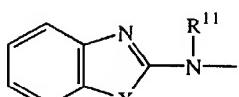
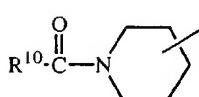


(a)

(b)

(c)

(d)



(e)

(f)

(g)

wherein

each X independently represents O, S or NR¹³;

R³ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

R⁴ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, mono- or di(C₁₋₆alkyl)amino or mono- or di(arylC₁₋₆alkyl)amino;

R⁵, R⁶, R⁷, R⁹, R¹¹, R¹² and R¹³ each independently are hydrogen or C₁₋₆alkyl;

R⁸ and R¹⁰ each independently are hydrogen, C₁₋₆alkyl or aryl; or

R⁴ and R⁵ taken together may form a bivalent radical -R⁴-R⁵- of formula

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	-CH ₂ -CH ₂ -CH ₂ -	(a-1);
5	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	(a-2);
	-CH=CH-CH ₂ -	(a-3);
	-CH ₂ -CH=CH-	(a-4) or
10	-CH=CH-CH=CH-	(a-5);
15	-S-CH ₂ -CH ₂ -	(a-6);
	-S-CH ₂ -CH ₂ -CH ₂ -	(a-7);
20	-S-CH=CH-	(a-8);
	-NH-CH ₂ -CH ₂ -	(a-9);
25	-NH-CH ₂ -CH ₂ -CH ₂ -	(a-10);
	-NH-CH=CH-	(a-11);
	-NH-CH=N-	(a-12);
30	-S-CH=N-	(a-13) or
	-CH=CH-O-	(a-14);

wherein one or where possible two or three hydrogen atoms in said radicals (a-6) to (a-14) each independently may be replaced by C₁₋₆alkyl or aryl; and
 35 aryl is phenyl or phenyl substituted with a halogen or C₁₋₆alkyl.

[0005] As used in the foregoing definitions the term halogen is generic to fluoro, chloro, bromo and iodo. The term C₁₋₄alkyl defines straight and branched saturated hydrocarbons, having from 1 to 4 carbon atoms such as, for example, 40 methyl, ethyl, propyl, butyl, 1-methylethyl, 1,1-dimethylethyl, 2-methylpropyl and the like. The term C₁₋₆alkyl is meant to include C₁₋₄alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, hexyl or the like. The term C₁₋₁₀alkyl is meant to include C₁₋₆alkyl radicals and the higher homologues thereof having 7 to 10 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl and the like. The term C₁₋₄alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-45 ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; the term C₁₋₆alkanediyl is meant to include C₁₋₄alkanediyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like; the term C₁₋₆alkylidene defines bivalent straight or branch chained alkylidene radicals having from 1 to 6 carbon atoms such as, for example, methylene, ethylidene, 1-propylidene, 1-butylidene, 1-pentylidene, 1-hexylidene and the like.

[0006] Also as used hereinafter, the term benzyl refers to phenylmethyl. Other names for the term γ -carboline are 5H-pyrido[4,3-b]indole, 3-azacarbazole and 3-azarbazole.

[0007] The addition salts as mentioned herein are meant to comprise the therapeutically active addition salt forms which the compounds of formula (I) are able to form with appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

[0008] The pharmaceutically acceptable addition salts as mentioned hereinabove are also meant to comprise the

therapeutically active non-toxic base, in particular, a metal or amine addition salt forms which the compounds of formula (I) are able to form. Said salts can conveniently be obtained by treating the compounds of formula (I) containing acidic hydrogen atoms with appropriate organic and inorganic bases such as, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted by treatment with an appropriate base or acid into the free acid or base form.

[0009] The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) are able to form and said solvates are meant to be included within the scope of the present invention. Examples of such solvates are, e.g. the hydrates, alcoholates and the like.

[0010] The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

[0011] The term stereochemically isomeric forms as used herein defines all the possible isomeric forms in which the compounds of formula (I) may occur. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure.

[0012] Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

[0013] Whenever used hereinafter, the term compounds of formula (I) is meant to include also the *N*-oxide forms, the pharmaceutically acceptable addition salts and all stereoisomeric forms.

[0014] A special group of compounds includes those compounds of formula (I) wherein one or more of the following restrictions apply:

- 25 1) R² is halogen, hydroxy, C₁₋₆alkyl or C₁₋₆alkyloxy;
- 2) n is 0 or 1;
- 3) Alk is C₁₋₄alkanediyl; preferably, Alk is 1,2-ethanediyl;
- 4) D is a radical of formula (a) wherein R³ is C₁₋₆alkyl, aryl or arylC₁₋₆alkyl; R⁴ is amino, mono- or di(C₁₋₆alkyl)amino, or mono- or di(arylC₁₋₆alkyl)amino; or -R⁴-R⁵- is a radical of formula (a-2) or (a-5) wherein one or two hydrogen atoms each independently may be replaced by halogen, C₁₋₆alkyl, trifluoromethyl or C₁₋₆alkyloxy, or -R⁴-R⁵- is a radical of formula (a-6), (a-7), (a-8), (a-11), (a-13) or (a-14) wherein one or where possible two hydrogen atoms each independently may be replaced by C₁₋₆alkyl;
- 5) D is a radical of formula (b) and R⁶ and R⁷ are suitably methyl;
- 6) D is a radical of formula (c) and R⁸ is suitably hydrogen, methyl or phenyl;
- 7) D is a radical of formula (d) and R⁹ is suitably hydrogen or methyl;
- 8) D is a radical of formula (e) wherein R¹⁰ is aryl; and suitably, R¹⁰ is 4-fluoro-phenyl, and the piperidine ring is connected in the 3- or 4-position to the remainder of the molecule;
- 9) D is a radical of formula (f) wherein X is S or NH and R¹¹ is hydrogen; or
- 10) D is a radical of formula (g) wherein X is S or NCH₃.

[0015] In case n is 1, the R² substituent is suitably positioned in the 6-, 7- or 8-position of the γ -carboline moiety, preferably in the 7- or 8-position, and R² is preferably chloro, fluoro, methyl, hydroxy or methoxy.

[0016] An interesting group of compounds includes those compounds of formula (I) wherein R¹ is hydrogen or aryl; R² is halogen or C₁₋₆alkyl; n is 0 or 1; Alk is C₁₋₄alkanediyl; D is a radical of formula (a) wherein R³ is C₁₋₆alkyl and -R⁴-R⁵- is a radical of formula (a-2), (a-5), (a-6), (a-7) or (a-8) wherein one or where possible two hydrogen atoms each independently may be replaced by C₁₋₆alkyl; or D is a radical of formula (d); or D is a radical of formula (f) wherein X is S and R¹¹ is hydrogen.

[0017] Another interesting group of compounds includes those compounds of formula (I) wherein R¹ is hydrogen or C₁₋₆alkyl; R² is halogen, C₁₋₆alkyl or C₁₋₆alkyloxy; n is 0 or 1; Alk is C₁₋₄alkanediyl; D is a radical of formula (a) wherein R⁴ is amino, mono- or di(C₁₋₆alkyl)amino or mono- or di(arylC₁₋₆alkyl)amino, or -R⁴-R⁵- is a radical of formula (a-2), (a-5), (a-6), (a-7), (a-8) or (a-11) wherein one or where possible two hydrogen atoms each independently may be replaced by C₁₋₆alkyl; or D is a radical of formula (d); or D is a radical of formula (g) wherein X is NR¹³.

[0018] Yet another interesting group of compounds includes those compounds of formula (I) wherein R² is halogen, hydroxy, C₁₋₆alkyl or C₁₋₆alkyloxy; n is 0 or 1, Alk is C₁₋₄alkanediyl; D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ is amino; or -R⁴-R⁵- is a radical of formula (a-2) or (a-5) wherein one or two hydrogen atoms each independently may be replaced by halogen, C₁₋₆alkyl, trifluoromethyl or C₁₋₆alkyloxy, or -R⁴-R⁵- is a radical of formula (a-6), (a-7), (a-8), (a-11), (a-13) or (a-14) wherein one or where possible two hydrogen atoms each independently may be replaced by C₁₋₆alkyl; or D is a radical of formula (d); or D is a radical of formula (f) wherein X is S or NR¹³ and R¹¹ is hydrogen; or

D is a radical of formula (g) wherein X is S or NR¹³.

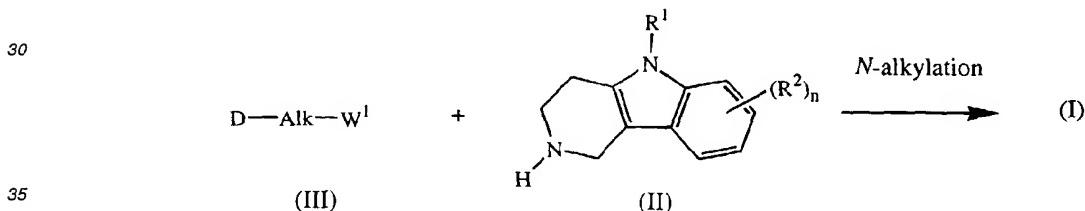
[0019] Still another interesting group of compounds includes those compounds of formula (I) wherein R¹ is hydrogen, C₁₋₆alkyl or aryl; R² is halogen, C₁₋₆alkyl or C₁₋₆alkyloxy; n is 0 or 1; Alk is C₁₋₄alkanediyl; D is a radical of formula (a) wherein R³ is C₁₋₆alkyl or arylC₁₋₆alkyl; or -R⁴-R⁵- is a radical of formula (a-5) wherein one or two hydrogen atoms each independently may be replaced by a halogen; or -R⁴-R⁵- is a radical of formula (a-6) or (a-8); or D is a radical of formula (d); or D is a radical of formula (e) wherein R¹⁰ is aryl; or D is a radical of formula (f) wherein X is S or NR¹³ and R¹¹ is hydrogen.

[0020] Particular compounds are those compounds of formula (I) wherein R¹ is hydrogen; n is 0 or n is 1 whereby R² is a halogen, C₁₋₆alkyl, or C₁₋₆alkoxy; Alk is 1,2-ethanediyl and D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ is amino; R⁵ is C₁₋₆alkyl; or -R⁴-R⁵- is a radical of formula (a-2), (a-5), (a-6), (a-7), (a-8) or (a-11) wherein one hydrogen atom may be replaced by C₁₋₆alkyl; or D is a radical of formula (g) wherein X is NR¹³ and R¹² is C₁₋₆alkyl, more in particular, wherein R¹ is hydrogen; n is 0 or n is 1 whereby R² is a chloro, methyl, or methoxy; Alk is 1,2-ethanediyl and D is a radical of formula (a) wherein R³ is methyl; R⁴ is amino; R⁵ is methyl; or -R⁴-R⁵- is a radical of formula (a-2), (a-5), (a-6), (a-7), (a-8) or (a-11) wherein one hydrogen atom may be replaced by methyl; or D is a radical of formula (g) wherein X is N-CH₃ and R¹² is methyl.

[0021] Other particularly interesting compounds are those compounds of formula (I) wherein R¹ is hydrogen; n is 0 or n is 1 whereby R² is a halogen or C₁₋₆alkyl; Alk is 1,2-ethanediyl and D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ and R⁵ are taken together to form -R⁴-R⁵- of formula (a-2), (a-5), (a-6), (a-7) or (a-8) wherein one hydrogen atom may be replaced by C₁₋₆alkyl; more in particular, wherein R¹ is hydrogen; n is 0 or n is 1 whereby R² is a chloro, fluoro or methyl; Alk is 1,2-ethanediyl and D is a radical of formula (a) wherein R³ is methyl; R⁴ and R⁵ are taken together to form -R⁴-R⁵- of formula (a-2), (a-5), (a-6), (a-7) or (a-8) wherein one hydrogen atom may be replaced by methyl.

[0022] A preferred set of compounds includes those compounds of formula (I) wherein R¹ is hydrogen, methyl, n-butyl phenyl, benzyl or 4-fluoro-phenyl.

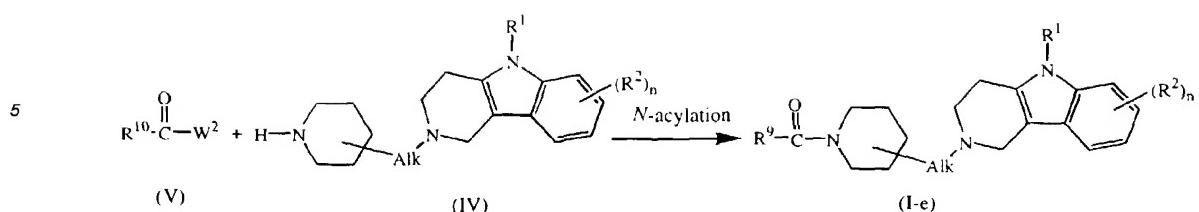
[0023] The compounds of formula (I) can generally be prepared by N-alkylating a 1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole derivative of formula (II) with an alkylating reagent of formula (III) following the procedure described in EP-A-0,037,265, EP-A-0,070,053, EP-A-0,196,132 and in EP-A-0,378,255.



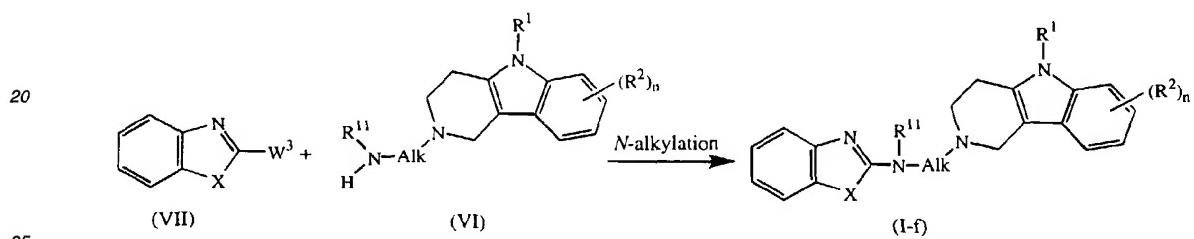
[0024] In particular, intermediate (III) wherein W¹ represents an appropriate reactive leaving group such as, for example, a halogen, e.g. chloro, bromo or iodo; a sulfonyloxy, e.g. methanesulfonyloxy, toluenesulfonyloxy, may be reacted with an intermediate of formula (II) in a reaction-inert solvent such as, for example, N,N-dimethylformamide or methyl-isobutylketon, in the presence of a suitable base such as, for example, sodiumcarbonate or triethylamine, and optionally in the presence of a catalyst such as, for example, potassium iodide.

[0025] In this and the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as extraction, crystallization, trituration and chromatography.

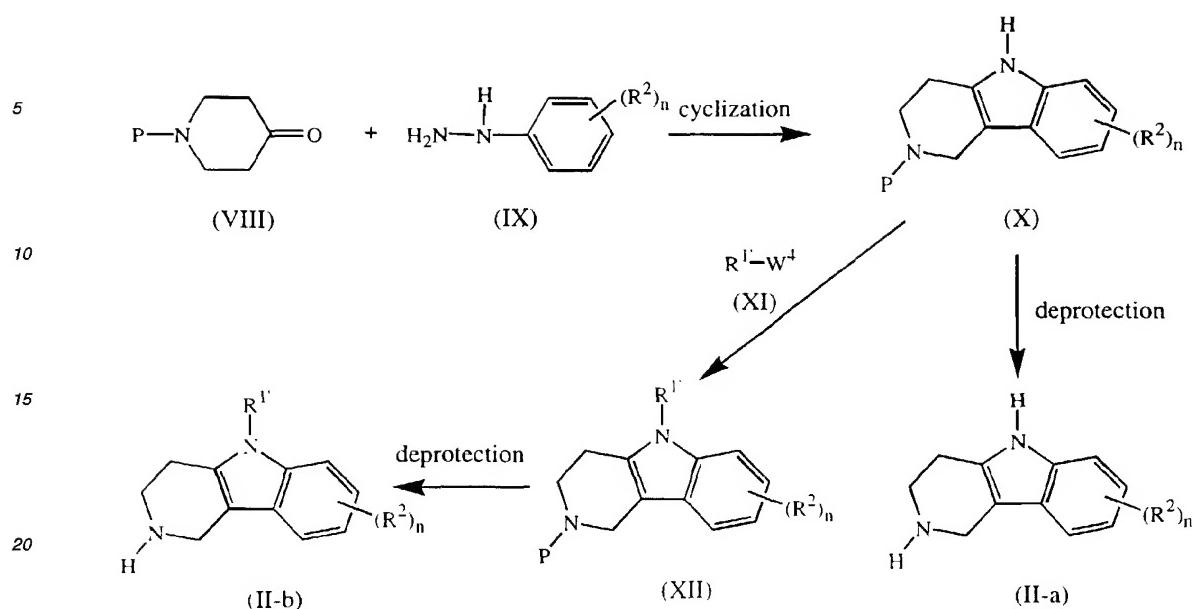
[0026] The compounds of formula (I) wherein D is a radical of formula (e) being represented by formula (I-e), may be prepared by N-acylating an intermediate of formula (IV) with an acyl derivative of formula (V) wherein W² is an appropriate reactive leaving group such as, for example, a halogen, in a reaction-inert solvent such as, for example, chloroform, in the presence of a suitable base such as, for example, sodium carbonate or triethylamine.



[0027] The compounds of formula (I) wherein D is a radical of formula (f), being represented by formula (I-f), can be prepared by *N*-alkylating an amine of formula (VI) with an intermediate of formula (VII) wherein W³ is an appropriate reactive leaving group such as, for example, a halogen, in a reaction-inert solvent such as, for example, ethanol or toluene, in the presence of a suitable base such as, for example, sodiumbicarbonate or sodiumcarbonate.

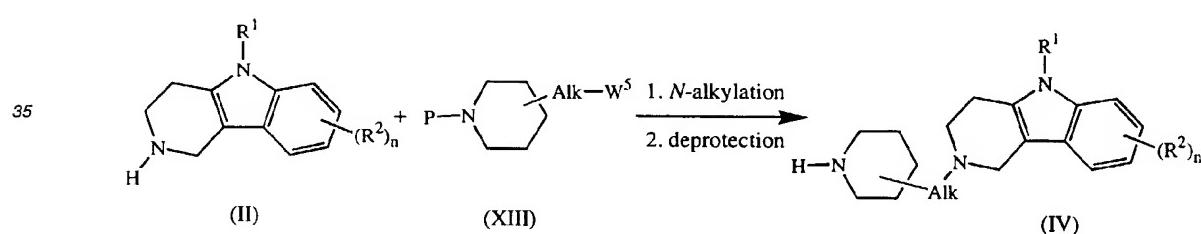


- [0028] Alternatively, intermediates (VI) may be *N*-alkylated with intermediates (VII) in the presence of copper.
- [0029] The compounds of formula (I) may be converted into each other following art-known functional group transformation reactions.
- [0030] The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenebroperoxic acid or halo substituted benzenebroperoxic acid, e.g. 3-chlorobenzenebroperoxic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.
- [0031] A number of intermediates and starting materials are commercially available or are known compounds which may be prepared according to art-known methodologies.
- [0032] For example, some of the intermediates of formula (III) and their preparations are described in EP-A-0,037,265, EP-A-0,070,053, EP-A-0,196,132 and in EP-A-0,378,255.
- [0033] Intermediates of formula (II) wherein R¹ is hydrogen, said intermediates being represented by formula (II-a), can generally be prepared by reacting an intermediate of formula (VIII) wherein P is a protective group such as, for example, an alkyloxycarbonyl group, with an intermediate of formula (IX) in a reaction-inert solvent, thus forming an intermediate of formula (X), and subsequently removing the protective group using art-known techniques such as, for instance, mixing the intermediate of formula (X) with potassium hydroxide in 2-propanol. Alternatively, the intermediate of formula (X) may be further reacted with a reagent of formula (XI) wherein R^{1'} is the same as R¹ but other than hydrogen and W⁴ is a suitable leaving group such as, for example, a halogen, in a suitable solvent such as, for example, hexamethylphosphorous triamide and the like, in the presence of an appropriate base such as, for example, sodium hydride, thus forming an intermediate of formula (XII) which may subsequently be deprotected using art-known techniques resulting in a compound of formula (II) wherein R¹ is other than hydrogen, said compounds being represented by formula (II-b).

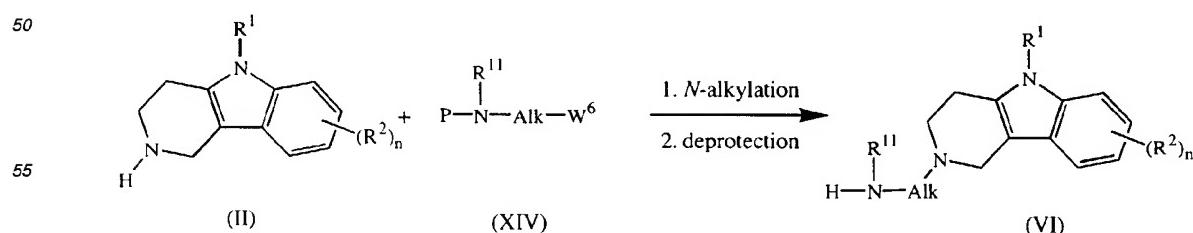


[0034] Intermediates of formula (IV) can be prepared by *N*-alkylating an intermediate of formula (II) with an intermediate of formula (XIII) wherein P is a protective group such as, for example, an alkyloxycarbonyl group, and W⁵ is a suitable leaving group such as, for example, a *p*-toluenesulfonyloxy group and the like, in a reaction-inert solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium carbonate.

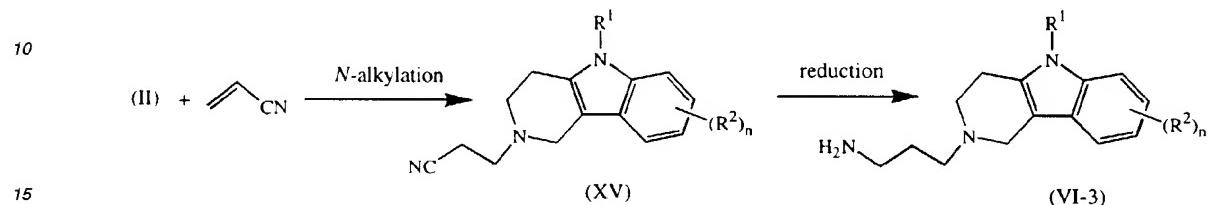
The thus formed intermediate may be deprotected using art-known deprotection techniques.



[0035] Intermediates of formula (VI) may be prepared by *N*-alkylating an intermediate of formula (II) with an intermediate of formula (XIV) wherein P is a protective group such as, for example, an alkyloxycarbonyl group, and W⁶ is a suitable leaving group such as, for example, a halogen, in a reaction-inert solvent such as, for example, methylisobutylketon, in the presence of a suitable base such as, for example, sodium carbonate, and optionally in the presence of a catalyst such as, for instance, potassium iodide. The thus formed intermediate may be deprotected using art-known deprotection techniques.

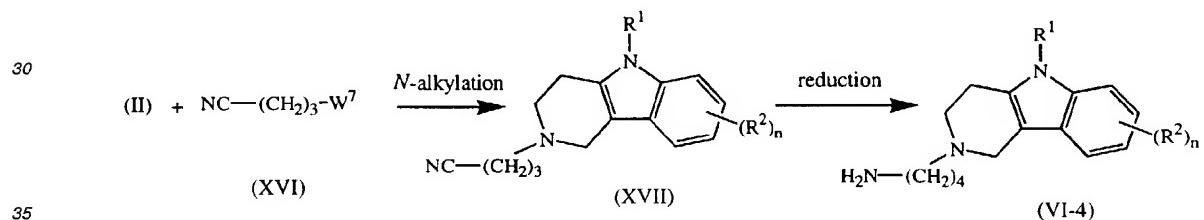


[0036] Intermediates of formula (VI) wherein Alk is 1,3-propanediyl and R¹¹ is hydrogen, said intermediates being represented by formula (VI-3) may suitably be prepared by reacting an intermediate of formula (II) with acrylonitrile in a reaction-inert solvent such as, for example, 2-propanol, and in the presence of a suitable catalyst such as, for example, a quaternary ammonium compound, e.g. Aliquat 336, thus forming a nitrile derivative of formula (XV) which may subsequently be reduced to the corresponding amine derivative using art-known reduction techniques as there are, for example, the use of hydrogen with Raney Nickel as a catalyst in methanol, optionally in the presence of ammonia.



20 [0037] Intermediates of formula (VI) wherein Alk is 1,4-butanediyl and R¹¹ is hydrogen, said intermediates being represented by formula (VI-4) may suitably be prepared by reacting an intermediate of formula (II) with an intermediate of formula (XVI) wherein W⁷ is a suitable leaving group such as, for example a halogen, in a reaction-inert solvent such as, for example, methylisobutylketon, and in the presence of a suitable base such as, for example, sodium carbonate, and optionally in the presence of a catalyst such as, for instance, potassium iodide, thus forming a nitrile derivative of formula (XVII) which may subsequently be reduced to the corresponding amine derivative using art-known reduction techniques as there are, for example, the use of hydrogen with Raney Nickel as a catalyst in methanol, optionally in the presence of ammonia.

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40 [0038] Some of the compounds of formula (I) and some of the intermediates in the present invention contain at least one asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers.

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[0039] Pure stereochemically isomeric forms of the compounds of formula (I) may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

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[0040] The compounds of formula (I), their pharmaceutically acceptable addition salts, stereochemically isomeric forms, or N-oxide forms thereof, all show a particular affinity for serotonin receptors, such as, 5-hydroxytryptamine receptors of the 5HT₁-and 5-HT₂-type, and have a antagonistic, partially antagonistic or agonistic effect thereon. Apart from their serotonergic receptor affinity, the present compounds also bind as ligands on the α₂- or dopamine receptors, or selectively inhibit serotonin reuptake. This broad-spectrum receptor-binding profile of the present compounds gives them a great therapeutic breadth, i.e. the present compounds are useful in controlling diseases which are characterized by disturbances of the serotonergic system, in particular with involvement of 5HT₂-type receptors. They are therefore

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suitable for treating disorders of the central nervous system including psychotic disorders such as, e.g. schizophrenia, tension and depression states, neuroses, psychoses, bipolar disorders, aggressive behaviour, anxiety and the like. Further, serotonin is a potent broncho- and vasoconstrictor and thus the present compounds acting as antagonists on the serotonin receptors may be used against hypertension and vascular disorders such as, migraine and migraine related disorders. In addition, compounds controlling the serotonergic system have been associated with a number of other properties such as, the suppression of appetite and promotion of weight loss, which may prove effective in combatting obesity; the alleviation of withdrawal symptoms in addicts trying to discontinue drinking and smoking habits; and also with gastrointestinal disorders such as, e.g. colonkinetic disturbances.

[0041] An additional feature of a particular group of the present compounds is that they have central α_2 -adrenoceptor activity. Central α_2 -adrenoceptor antagonists are known to increase noradrenaline release by blocking presynaptic α_2 -receptors which exert an inhibiting control over the release of the neurotransmitter. By increasing the noradrenaline concentrations, α_2 -antagonists can be used particularly for the treatment or prophylaxis of depression, and are also potentially useful in the treatment of Alzheimer's disease and dementia as it is known that α_2 -antagonists promote the release of acetylcholine (Tellez et al. 1997, J. Neurochem. 68:778-785).

[0042] Also the inhibitory activity of a particular group of the present compounds on the reuptake of serotonin contributes to the effectiveness to treat tension and depression states.

[0043] Another particular group of the present compounds exhibits a pronounced affinity for dopaminergic receptors which in combination with an affinity for serotonergic receptors is of great therapeutic potential in the treatment of psychosis.

[0044] The 5-HT₂ receptor-binding profile of the compounds of formula (I) is discussed in the pharmacological example C.1. Further, the serotonergic properties of the present compounds may be evidenced by the "apomorphine, tryptamine, norepinephrine (ATN) test in rats", described in Arch. Int. Pharmacodyn., 227, 238-253 (1977).

[0045] The present invention thus relates to compounds of formula (I) as defined hereinabove for use as a medicine. Also, the present invention relates to the use of the present compounds for the manufacture of a medicament for treating depression, anxiety and psychosis.

[0046] In view of the usefulness of the subject compounds in the treatment or prevention of the above-mentioned disorders, the present invention provides a method of treating warm-blooded animals suffering from such disorders, in particular depression, anxiety and psychosis, said method comprising the systemic administration of a therapeutically effective amount of a compound of formula (I), a *N*-oxide or a pharmaceutically acceptable addition salt thereof, effective in treating disorders associated with the serotonergic system

[0047] In general it is contemplated that an effective therapeutic daily amount would be from about 0.01 mg/kg to about 4 mg/kg body weight. The exact dosage to be used in the treatment of any of the above-mentioned disorders must be subjectively determined by the attending physician. The variables involved include the severity of the disorder and the size, age and response pattern of the patient.

[0048] For administration purposes, the subject compounds may be formulated into various pharmaceutical compositions comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound of formula (I). To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in addition salt or in free acid or base form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders,

pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of formula (I) may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin.

Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Addition salts of (I) due to their increased water solubility over the corresponding free base or free acid form, are obvi-

ously more suitable in the preparation of aqueous compositions.

[0049] It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

[0050] The following examples are intended to illustrate and not to limit the scope of the present invention.

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Experimental part

A. Preparation of the intermediates

Example A1

[0051]

- a) A mixture of ethyl 4-oxo-1-piperidinecarboxylate (0.23mol) and 4-(benzyloxy)phenyl hydrazine (0.23mol) in ethanol (400ml) was stirred and refluxed for 5 hours. The reaction mixture was stirred overnight at room temperature. The solid was filtered off and washed on filter with H₂O/2-propanol (200ml). The precipitate was dissolved in CHCl₃ (300ml), washed with water (2x50ml), dried, filtered and the solvent was evaporated. The residue was crystallized from CH₃CN (300ml) and cooled to 0°C. The resulting precipitate was filtered off and dried, yielding 51.0g (63%) of ethyl 1,3,4,5-tetrahydro-8-(phenylmethoxy)-2H-pyrido[4,3-b] indole-2-carboxylate (intermediate 1).
- b) A mixture of intermediate (1) (0.09 mol) in N,N-dimethylformamide (200 ml) was stirred at 10 °C under a N₂ flow. Sodium hydride (60%; 0.1 mol) was added portionwise. The mixture was stirred for 1 hour at room temperature, then it was cooled to 5 °C. Benzylbromide (0.1 mol) was added dropwise. Stirring was continued for 2 hours. The mixture was cooled to 10 °C and poured out into cold water (500 ml). This mixture was extracted with CH₂Cl₂ (2 x 250 ml). The separated organic layer was washed with water (100 ml), dried, filtered and the solvent was evaporated. The solid residue was washed with CH₃CN (50 ml), cooled and the resulting precipitate was filtered off and dried, yielding 30.0 g (76%) of ethyl 1,3,4,5-tetrahydro-8-(phenylmethoxy)-5-(phenyl-methyl)-2H-pyrido[4,3-b]indole-2-carboxylate (intermediate 2).
- c) A mixture of intermediate (2) (0.067 mol) and KOH (0.67 mol) in 2-propanol (250 ml) was stirred and refluxed for 5 hours. The solvent was evaporated. Water (300 ml) was added and the organic solvent was removed azeotropically. The precipitate was filtered off and dissolved in CH₂Cl₂ (300 ml). The organic solution was dried, filtered and the solvent was evaporated. The residue was washed in CH₃CN (50 ml), filtered off and dried, yielding 22.7 g (92%) of 2,3,4,5-tetrahydro-8-(phenylmethoxy)-5-(phenylmethyl)-1H-pyrido[4,3-b]indole (intermediate 3).
- d) A mixture of intermediate (3) (0.062 mol) in methanol (400 ml) and tetrahydrofuran (100 ml) was warmed to 50 °C until complete dissolution. This solution was hydrogenated at 50 °C with palladium-on-charcoal (10%; 5 g) as a catalyst. After uptake of H₂ (1 equivalent), hydrogenation was stopped and acetic acid (50 ml) was added to dissolve the precipitate. The catalyst was filtered off and the filtrate was acidified with HCl/2-propanol (30 ml). The precipitate was filtered off, suspended in CH₃CN (100 ml), filtered off and dried, yielding 14.5 g (74%) of 2,3,4,5-tetrahydro-5-(phenylmethyl)-1H-pyrido[4,3-b]indol-8-ol monohydrochloride (intermediate 8).

Example A.2

[0052]

- a) A mixture of 2,3,4,5-tetrahydro-8-methyl-1H-pyrido[4,3-b]indole, (0.079 mol), ethyl 3-chloropropanamide (0.097 mol), Na₂CO₃ (15 g) and potassium iodide (0.1 g) in methyl isobutyl ketone (350 ml) was stirred and refluxed overnight. The reaction mixture was filtered and the filtrate was evaporated, yielding 20 g (80%) of ethyl [3-(1,3,4,5-tetrahydro-8-methyl-2H-pyrido[4,3-b]indol-2-yl)propyl]carbamate (intermediate 9).
- b) A mixture of intermediate (9) (0.063 mol) and KOH (35 g) in 2-propanol (300 ml) was stirred and refluxed overnight. The solvent was evaporated. The residue was stirred in water and this mixture was extracted with methyl isobutyl ketone. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/(CH₃OH/NH₃) 85/15). The pure fractions were collected and the solvent was evaporated, yielding 7 g (46%) of 1,3,4,5-tetrahydro-8-methyl-2H-pyrido[4,3-b]indole-2-propanamine (intermediate 10).

Example A.3

[0053]

- 5 a) A mixture of 2,3,4,5-tetrahydro-5-methyl-1*H*-pyrido[4,3-*b*]indole (0.07mol), acrylonitrile (0.14mol) and Aliquat 336 (3 drops) in 2-propanol (150ml) was stirred and refluxed for 30 minutes. The reaction mixture was cooled on an ice-bath and the resulting precipitate was filtered off, washed with diisopropyl ether (50ml) and dried, yielding 14.5g (87%) of 1,3,4,5-tetrahydro-5-methyl-2*H*-pyrido[4,3-*b*]indole-2-propanenitrile (intermediate 14).
10 b) A mixture of intermediate (14) (0.06mol) in NH₃/CH₃OH (400ml) was hydrogenated at 20°C with Raney Nickel (3g) as a catalyst. After uptake of hydrogen (2 equivalents), the catalyst was filtered off and the filtrate was evaporated, yielding 14.6 g of 1,3,4,5-tetrahydro-5-methyl-2*H*-pyrido[4,3-*b*]indole-2-propanamine (intermediate 15).

Example A.4

[0054]

- 15 a) A mixture of 1,2,3,4-tetrahydro-5*H*-pyrido[4,3-*b*]indole (0.2 mol) and 1-(phenylmethyl)-4-piperidinone (0.2 mol) in methanol (700 ml) was hydrogenated at 50 °C with palladium-on-charcoal (10%; 3 g) as a catalyst in the presence of thiophene (4%; 2 ml). After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated, yielding 69 g 2,3,4,5-tetrahydro-2-[1-(phenylmethyl)-4-piperidinyl]-1*H*-pyrido[4,3-*b*]indole (intermediate 23).
20 b) A mixture of intermediate (23) (0.20 mol) in methanol (700 ml) was hydrogenated at 50 °C with palladium-on-charcoal (10%; 3 g) as a catalyst. After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from diisopropylether/CH₃CN. The precipitate was filtered off and dried yielding 44.1 g (86.4%) of 2,3,4,5-tetrahydro-2-(4-piperidinyl)-1*H*-pyrido[4,3-*b*]indole (intermediate 24).

[0055] The following intermediates were prepared according to one of the above examples.

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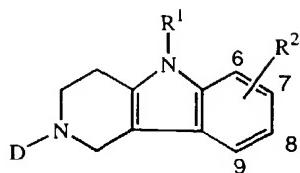
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Table 1

Interm. No.	Ex. No.	D	R ¹	R ²	Physical data melting point in °C
4	A1c	H	CH ₃	H	HCl
5	A1c	H	(CH ₂) ₃ -CH ₃	H	HCl
6	A1c	H	C ₆ H ₅ -CH ₂ -	H	HCl; mp. 242.5°C
7	A1c	(CH ₂) ₄ -NH ₂	H	7-Cl	-
8	A1d	H	H	8-OH	HCl
11	A2		CH ₃	H	100°C
12	A2	(CH ₂) ₃ -NH ₂	H	8-Cl	-
13	A2	(CH ₂) ₃ -NH ₂	H	7-Cl	-
16	A3	(CH ₂) ₃ -NH ₂	H	H	-
17	A3	(CH ₂) ₄ -NH ₂	H	H	-
18	A3	(CH ₂) ₄ -NH ₂	H	8-F	108.4°C
19	A3	(CH ₂) ₃ -NH ₂	H	8-F	-
20	A3	(CH ₂) ₄ -NH ₂	H	8-CH ₃	-
21	A3	(CH ₂) ₄ -NH ₂	H	8-OCH ₃	-
22	A3	(CH ₂) ₃ -NH ₂	H	8-OCH ₃	-
25	A1c		H	8-F	-

B. Preparation of the compounds of formula (I)Example B.1

[0056]

- a) A mixture of 6-(2-bromoethyl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidin-5-one monohydrobromide (0.017 mol), intermediate 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-ol monohydrochloride (0.015 mol) and sodium carbonate (0.075 mol) in methylisobutyl ketone (250 ml) was stirred and refluxed for 18 hours. The mixture was filtered hot and the filtrate was evaporated. The residue was crystallized from N,N-dimethylformamide (20 ml). The precipitate was filtered off, washed on a filter with methanol (5 ml) and dried, yielding 0.8 g (14%) of 3,7-dimethyl-6-[2-(1,3,4,5-tetrahydro-8-hydroxy-2H-pyrido[4,3-b]indol-2-yl)ethyl]-5H-thiazolo[3,2-a]pyrimidin-5-one (compound 59).
- b) 7-[2-(8-fluoro-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indol-2-yl)ethyl]-3,4-dihydro-8-methyl-2H,6H-pyrimido[2,1-b][1,3]-thiazin-6-one (compound 2) was prepared in a similar way as compound 59 but a catalytic amount of sodium methoxide (30 % solution) was added to the reaction mixture.

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- c) 6,7,8,9-tetrahydro-2-methyl-3-[2-(1,3,4,5-tetrahydro-5-methyl-2H-pyrido[4,3-b]indol-2-yl)ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one (compound 81) was prepared in a similar way as compound 59 but a catalytic amount of potassium iodide was added to the reaction mixture.
- 5 d) (\pm)-1-(4-fluorobenzoyl)-3-[(1,3,4,5-tetrahydro-5-methyl-2H-pyrido[4,3-b]indol-2-yl)methyl]piperidine (E)-2-butenedioate (1:1) (compound 130) was prepared in a similar way as compound 59 but N,N-dimethylformamide was used as reaction-inert solvent instead of methylisobutylketon.
- e) 3-[2-(7-chloro-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indol-2-yl)ethyl]-9-methoxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound 20) was prepared in a similar way as compound 59 but triethylamine was used instead of sodium carbonate.
- 10 f) 2,3-dihydro-7-methyl-6-[2-(1,3,4,5-tetrahydro-8-hydroxy-2H-pyrido[4,3-b]indol-2-yl)ethyl]-5H-thiazolo[3,2-a]pyrimidin-5-one (compound 62) was prepared in a similar way as compound 130 but triethylamine was used instead of sodium carbonate.
- 15 g) A mixture of 6-(2-chloroethyl)-2,7-dimethyl-5H-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (4.2 g), 1,2,3,4-tetrahydro-5H-pyrido[4,3-b]indole (2.65 g), sodium bicarbonate (2 g), potassium iodide (0.1 g) in 1-butanol (122 ml) was refluxed for 20 hours. The reaction mixture was filtered while hot and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CHCl₃/CH₃OH 95/5). The solvent of the desired fraction was evaporated and the residue was crystallized from acetonitrile, yielding 1.6 g (28.1%) of 6-[2-(1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indol-2-yl)ethyl]-2,7-dimethyl-5H-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (compound 42).

20 Example B.2

[0057] A mixture of intermediate 25 (0.01 mol) and triethylamine (0.011 mol) in chloroform (150 ml) was stirred at room temperature. 4-fluoro-benzoylchloride (0.011 mol) was added. The reaction mixture was stirred for 60 minutes at room temperature. Water (50 ml) was added and the mixture was stirred for 10 minutes. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was solidified in CH₃CN (40 ml), filtered off and dried, yielding 2.7 g (66%) of (\pm)-1-(4-fluorobenzoyl)-3-[(8-fluoro-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indol-2-yl)methyl]piperidine (compound 132).

30 Example B.3

[0058]

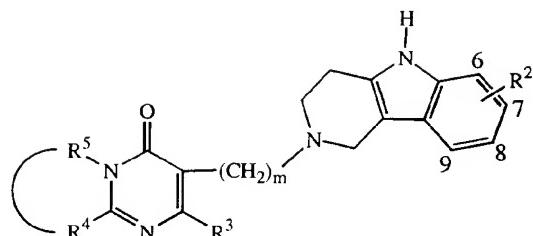
- a) A mixture of 2-chloro-benzothiazole (0.02 mol), intermediate 17 (0.018 mol) and sodiumbicarbonate (0.040 mol) in ethanol (120 ml) was stirred and refluxed overnight. The mixture was cooled and filtered until clear. The filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 90/10). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was filtered off and dried, yielding 3.4 g (50%) of N-2-benzothiazolyl-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-butanamine (compound 120).
- 35 b) N-2-benzothiazolyl-8-fluoro-1,3,4,5,-tetrahydro-2H-pyrido[4,3-b]indole-2-butanamine (compound 121) was prepared in a similar way as compound 120 but sodium carbonate was replaced by sodiumbicarbonate and ethanol was replaced by toluene.

40 Example B.4

45 [0059] A mixture of 2-chloro-1H-benzimidazole (0.015mol), intermediate 15 (0.015mol) and copper (0.015mol) was stirred in an oil bath at 180°C. The mixture was cooled and the product was dissolved in CHCl₃ (50ml). The solution was filtered over dicalite and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CHCl₃/(CH₃OH/NH₃) 95/5). The pure fractions were collected and the solvent was evaporated. The residue was dissolved in CH₃CN (50ml) and converted into the hydrochloric acid salt (1:2) with HCl/2-propanol. The salt was filtered off, washed on filter with cold CH₃CN (20ml), then dried, yielding 1.1 g (17%) of N-1H-benzimidazol-2-yl-1,3,4,5-tetrahydro-5-methyl-2H-pyrido [4,3-b]indole-2-propanamine dihydrochloride.hemihydrate (compound 118).

[0060] Tables 2 to 8 list compounds of formula (I) which were prepared according to one of the above examples as indicated in the column "Ex No.".

Table 2



Co. No.	Ex. No.	R ²	R ³	-R ⁴ -R ⁵ -	m	Physical data melting point in °C
1	B1c	8-F	CH ₃	-CH=CH-CH=CH-	2	225.5°C
2	B1b	8-F	CH ₃	-S-CH ₂ -CH ₂ -CH ₂ -	2	208.3°C
3	B1b	8-F	CH ₃	-S-CH ₂ -CH ₂ -	2	224.1°C
4	B1c	8-F	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	>300°C
5	B1b	8-F	CH ₃	-S-CH=C(CH ₃)-	2	250.7°C
6	B1c	8-F	CH ₃	-S-CH=CH-	2	218.1°C
7	B1c	7-Cl	CH ₃	-S-CH=CH-	2	219.6°C
8	B1b	7-Cl	CH ₃	-S-CH=C(CH ₃)-	2	199.2°C
9	B1c	7-Cl	CH ₃	-CH=CH-CH=CH-	2	214.9°C
10	B1c	7-Cl	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	202.4°C
11	B1b	7-Cl	CH ₃	-S-CH ₂ -CH ₂ -CH ₂ -	2	227.0°C
12	B1b	7-Cl	CH ₃	-S-CH ₂ -CH ₂ -	2	240.5°C
13	B1c	7-Cl	CH ₃	-C(CH ₃)=CH-CH=CH-	2	
14	B1c	7-Cl	CH ₃	-CH=CH-CBr=CH-	2	296°C
15	B1a	7-Cl	CH ₃	-CCl=CH-C(CF ₃)=CH-	2	260°C
16	B1c	7-Cl	CH ₃	-CH=CH-C(CH ₃)=CH-	2	
17	B1c	7-Cl	CH ₃	-CH=CH-CCl=CH-	2	278°C
18	B1c	7-Cl	CH ₃	-CH=C(CH ₃)-CH=C(CH ₃)-	2	268°C; fumaric acid
19	B1a	7-Cl	CH ₃	-CCl=CH-CCl=CH-	2	268°C
20	B1e	7-Cl	CH ₃	-C(OCH ₃)=CH-CH=CH-	2	
21	B1c	7-Cl	CH ₃	-CH=CH-CH=C(CH ₃)-	2	
22	B1c	7-Cl	CH ₃	-CH=C(CH ₃)-CH=CH-	2	
23	B1b	8-Cl	CH ₃	-S-CH=C(CH ₃)-	2	230.4°C
24	B1b	8-Cl	CH ₃	-S-CH ₂ -CH ₂ -CH ₂ -	2	241.2°C
25	B1c	8-Cl	CH ₃	-S-CH=CH-	2	215.8°C
26	B1b	8-Cl	CH ₃	-S-CH ₂ -CH ₂ -	2	218.3°C

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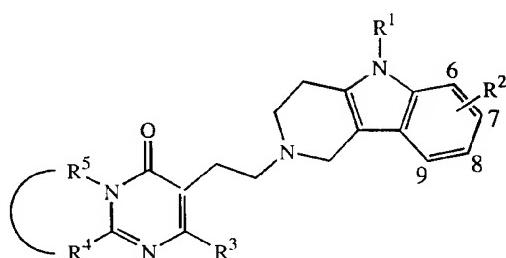
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	Co. No.	Ex. No.	R ²	R ³	-R ⁴ -R ⁵ -	m	Physical data melting point in °C
5	27	B1c	8-Cl	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	217.1°C
	28	B1c	8-Cl	CH ₃	-CH=CH-CH=CH-	2	273.4°C
	29	B1c	6-CH ₃	CH ₃	-S-CH ₂ -CH ₂ -CH ₂ -	2	204.7°C
10	30	B1c	8-CH ₃	CH ₃	-S-CH=CH-	2	197.9°C
	31	B1c	8-CH ₃	CH ₃	-S-CH ₂ -CH ₂ -	2	153.8°C; H ₂ O (2:1)
15	32	B1c	8-CH ₃	CH ₃	-S-CH=C(CH ₃)-	2	213.4°C
	33	B1c	8-CH ₃	CH ₃	-S-CH ₂ -CH ₂ -CH ₂ -	2	216.9°C
	34	B1c	8-CH ₃	CH ₃	-CH=CH-CH=CH-	2	209.8°C
	35	B1c	8-CH ₃	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	192.8°C
20	36	B1c	8-CH ₃	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	fumaric acid
	37	B1c	H	CH ₃	-CH=CH-CH=CH-	2	193.4°C
	38	B1c	H	CH ₃	-S-CH=CH-	2	212.8°C
25	39	B1a	H	CH ₃	-S-CH=C(CH ₃)-	2	274.1°C
	40	B1c	H	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	189.1°C
	41	B1a	H	CH ₃	-S-CH ₂ -CH ₂ -	2	208.3°C
	42	B1g	H	CH ₃	-S-C(CH ₃)=N-	2	270.2°C
30	43	B1c	H	CH ₃	-N(CH ₃)-CH=CH-	2	229.9°C
	44	B1a	H	CH ₃	-S-CH ₂ -CH ₂ -CH ₂ -	3	209.2°C
	45	B1a	H	CH ₃	-S-CH ₂ -CH ₂ -	3	186.7°C
35	46	B1a	H	CH ₃	-S-CH=C(CH ₃)-	3	178.6°C
	47	B1c	H	CH ₃	-C(CH ₃)=CH-CH=CH-	3	200.2°C
	48	B1a	H	CH ₃	-CH=CH-CH=CH-	3	
	49	B1a	H	CH ₃	-S-CH=CH-	3	fumaric acid (2:1)
40	50	B1c	H	phenyl	-CH=CH-CH=CH-	2	188.2°C
	51	B1c	H	benzyl	-CH=CH-CH=CH-	2	193.5°C
	52	B1c	8-OCH ₃	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	202.3°C
45	53	B1c	8-OCH ₃	CH ₃	-CH=CH-CH=CH-	2	173.1°C
	54	B1b	8-OCH ₃	CH ₃	-S-CH=C(CH ₃)-	2	274.5°C
	55	B1b	8-OCH ₃	CH ₃	-S-CH ₂ -CH ₂ -	2	189.2°C
	56	B1b	8-OCH ₃	CH ₃	-S-CH ₂ -CH ₂ -CH ₂ -	2	235.7°C
50	57	B1c	8-OCH ₃	CH ₃	-S-CH=CH-	2	141.5°C
	58	B1c	8-OH	CH ₃	-CH=CH-CH=CH-	2	219.2°C

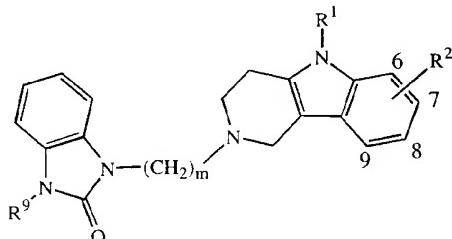
Co. No.	Ex. No.	R ²	R ³	-R ⁴ -R ⁵ -	m	Physical data melting point in °C	
5	59	B1a	8-OH	CH ₃	-S-CH=C(CH ₃)-	2	254.6°C
10	60	B1c	8-OH	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	214.1°C
15	61	B1c	8-OH	CH ₃	-S-CH=CH-	2	198.7°C
20	62	B1f	8-OH	CH ₃	-S-CH ₂ -CH ₂ -	2	243.2°C
25	63	B1f	8-OH	CH ₃	-S-CH ₂ -CH ₂ -CH ₂ -	2	218.6°C
30	64	B1c	8-OH	CH ₃	-CH=CH-CH=CH-	3	207.5°C
35	65	B1c	8-OH	CH ₃	-CH=C(CH ₃)-O-	2	168.9°C

Table 3

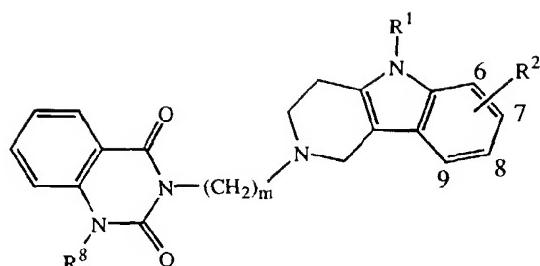
Co. No.	Ex. No.	R ¹	R ²	R ³	-R ⁴ -R ⁵ -	Physical data melting point in °C	
30	66	B1b	4-F-phenyl	8-F	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	174.6°C
35	67	B1a	4-F-phenyl	8-F	CH ₃	-S-CH ₂ -CH ₂ -	186.4°C
40	68	B1a	4-F-phenyl	8-F	CH ₃	-S-CH=C(CH ₃)-	121.7°C
45	69	B1c	benzyl	H	CH ₃	-CH=CH-CH=CH-	156.6°C
50	70	B1c	benzyl	H	CH ₃	-S-CH=CH-	165.2°C
55	71	B1c	benzyl	H	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	132.2°C
60	72	B1c	benzyl	H	CH ₃	-S-CH ₂ -CH ₂ -	157.9°C
65	73	B1c	benzyl	8-OH	CH ₃	-CH=CH-CH=CH-	158.8°C
70	74	B1c	benzyl	8-OH	CH ₃	-S-CH=CH-	134.9°C
75	75	B1c	benzyl	8-OH	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	130.3°C
80	76	B1c	benzyl	8-OH	CH ₃	-CH=CH-CH=CH-	212.0°C
85	77	B1c	benzyl	H	phenyl	-CH=CH-CH=CH-	183.2°C
90	78	B1c	benzyl	H	benzyl	-CH=CH-CH=CH-	213.3°C; fumaric acid
95	79	B1c	CH ₃	H	phenyl	-CH=CH-CH=CH-	151.2°C

Co. No.	Ex. No.	R ¹	R ²	R ³	-R ⁴ -R ⁵ -	Physical data melting point in °C
80	B1c	CH ₃	H	benzyl	-CH=CH-CH=CH-	151.8°C
81	B1c	CH ₃	H	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	157.7°C
82	B1c	CH ₃	H	CH ₃	-CH=CH-CH=CH-	117.6°C
83	B1c	CH ₃	H	CH ₃	-S-CH ₂ -CH ₂ -	182.4°C
84	B1c	CH ₃	H	CH ₃	-S-CH=CH-	152.9°C
85	B1c	(CH ₂) ₃ CH ₃	H	CH ₃	-S-CH ₂ -CH ₂ -	158.8°C; fumaric acid (2:1); H ₂ O
86	B1c	phenyl	H	CH ₃	-S-CH ₂ -CH ₂ -	199.7°C
87	B1c	phenyl	H	CH ₃	-S-CH=CH-	172.5°C
88	B1c	phenyl	H	CH ₃	-CH=CH-CH=CH-	157.3°C
89	B1c	phenyl	H	CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	163.8°C

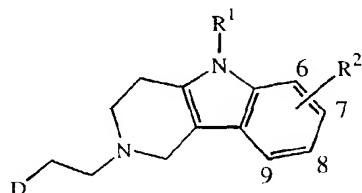
Table 4



Co. No.	Ex. No.	R ¹	R ²	R ⁹	m	Physical data melting point in °C
90	B1a	4-F-phenyl	8-F	H	3	162.7°C
91	B1c	H	8-F	H	2	207.0°C
92	B1c	H	8-F	H	3	164.1°C
93	B1c	H	7-Cl	H	3	207.5°C
94	B1c	H	7-Cl	H	2	209.7°C; HCl
95	B1c	H	8-Cl	H	3	151.2°C
96	B1c	H	8-Cl	H	2	231.5°C
97	B1c	H	8-F	CH ₃	2	162.4°C
98	B1c	H	8-OCH ₃	H	3	207.3°C
99	B1c	H	8-OCH ₃	H	2	202.4°C
100	B1c	H	8-CH ₃	H	2	209.3°C
101	B1c	H	6-CH ₃	H	2	215.1°C
102	B1a	H	H	H	2	208.6°C

Table 5

Co. No.	Ex. No.	R ¹	R ²	R ⁸	m	Physical data melting point in °C
103	B1a	H	8-F	H	2	227.2°C
104	B1c	H	H	CH ₃	2	240.0°C
105	B1c	H	H	phenyl	2	173.9°C
106	B1c	benzyl	H	H	2	201.9°C
107	B1c	benzyl	H	H	3	213.6°C
108	B1c	phenyl	H	H	2	208.9°C

Table 6

Co. No.	Ex. No.	R ¹	R ²	D	Physical data melting point in °C
109	B1c	4-F-phenyl	8-F		196.1°C
110	B1c	H	8-F		255.6°C
111	B1c	H	H		240.0°C

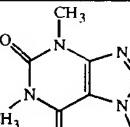
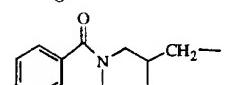
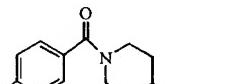
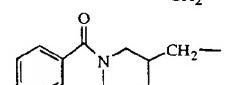
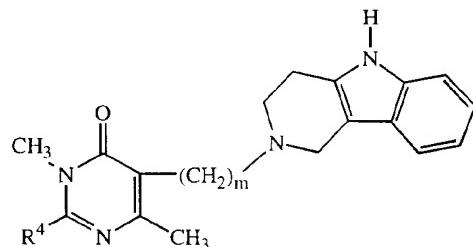
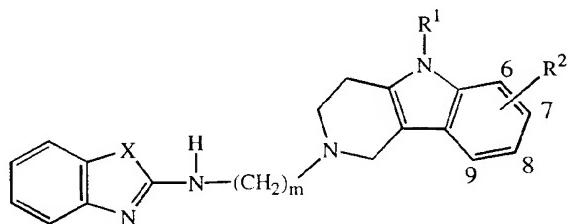
Co. No.	Ex. No.	R ¹	R ²	D	Physical data melting point in °C
112	B1c	H	H		215.5°C
130	B1d	CH ₃	H		202.5°C; fumaric acid
131	B2	CH ₃	H		148.0°C
132	B2	H	8-F		153.5°C

Table 7



Co. No.	Ex. No.	R ⁴	m	Physical data melting point in °C
113	B1c	NH ₂	2	190.7°C; H ₂ O (2:1)
114	B1c	NH ₂	3	170.6°C
115	B1c	NH(CH ₃)	2	139.9°C; H ₂ O
116	B1c	NH(benzyl)	2	199.9°C
117	B1a	NH(CH ₂ CH ₂ CH ₃)	3	133.9°C

Table 8



Co. No.	Ex. No.	R ¹	R ²	X	m	Physical data melting point in °C	
5	118	B.4	CH ₃	H	NH	3	257.1°C; H ₂ O (2:1); HCl (1:2)
10	119	B3a	H	H	S	3	211.1°C; fumaric acid (2:1)
120	B3a	H	H	S	4	179.8°C	
121	B3b	H	8-F	S	4	177.6°C	
122	B3b	H	8-F	S	3	164.8°C	
123	B3b	H	8-OCH ₃	S	4	187.5°C; fumaric acid (1:2)	
124	B3b	H	8-OCH ₃	S	3	193.7°C	
125	B3a	H	8-CH ₃	S	3	209.8°C; HCl (1:2)	
126	B3a	H	8-CH ₃	S	4	226.2°C; HCl (1:2)	
20	127	B3a	H	8-Cl	S	3	150.4°C
128	B3b	H	7-Cl	S	3	228.6°C; fumaric acid (2:3)	
129	B3b	H	7-Cl	S	4	202.1°C; fumaric acid	

25

C. Pharmacological example30 Example C.1

[0061] 5HT₂ receptors were measured by radioligand binding studies either in homogenates from rat brains or in a membranes fraction prepared from L929sA cells (mouse fibro carcinoma cells), stably transfected with human 5HT_{2A} receptor cDNA.

35

Sample preparation*5HT₂ binding in rat frontal cortex*

40 [0062] 5HT₂ receptors were measured in a rat frontal cortex membrane fraction. Therefore wistar rats were killed by decapitation, brains were removed and frontal cortex was dissected. The frontal cortex was homogenized in Tris-HCL buffer 50 mM pH7.7. The homogenate was centrifuged at 23.000 g for 10 minutes. The resulting pellet was washed twice by resuspension and recentrifugation and the pellet was finally suspended in Tris-HCL buffer 50 mM pH7.7 in a dilution of 100 (vol/wet weight of tissue). 400 µl of the homogenate was incubated with 1 nM [³H]ketanserin in a total 45 incubation volume of 0.5 ml for 30 minutes at 37 ° C. The incubation was stopped by rapid filtration using a manual filtration manifold. The filters were rinsed twice with ice-cold buffer and were counted in a liquid scintillation counter. Non-specific binding was determined in the presence of 1 µM methysergide.

5HT_{2A} binding in L929sA cells

50

[0063] L929sA cells expressing human 5HT_{2A} receptors were cultured in Petri dishes in DMEM medium (Gibco cat.nr. 41965-039) enriched with 5 % heat inactivated fetal calf serum and in the presence of penicillin and streptomycin sulphate. 24 h before collection, cells were induced with m-interferon-b (1000 U/ml medium). Cells were collected by scrapping and centrifugation at low speed (5 minutes at 1500 g). The cells were homogenized and centrifuged for 10 minutes at 23.000 g. The resulting pellet was diluted in Tris-HCl 50 mM pH 7.7 and stored at -70 ° C. On the day of the experiment, a vial was thawed and diluted in Tris-HCl buffer. 5HT_{2A} receptors are labeled with 0.1 nM [¹²⁵I] 4-amino-N-[1-[3-(4-fluorophenoxy)propyl]4-methyl-4-piperidinyl]-2-methoxybenzamide dihydrate. Membranes (0.2ml) were incubated with the radioligand for 60 minutes at 37 ° C in a total volume of 0.25 ml. The reaction was stopped by rapid fil-

tration and the filter rounds were counted in an auto-gamma spectrophotometer.

Data analysis

- 5 [0064] Counting data from assays in the presence of test compound were automatically expressed as percent of total binding measured in the absence of test compound. Therefrom, the pIC₅₀ (-log IC₅₀)-values (IC₅₀ = concentration in M inhibiting 50 % of the specific radioligand binding or neurotransmitter uptake) were derived and are listed in Table 9 (a "-" means "not measured").

10

Table 9

15	Comp. No.	5HT ₂ - binding	5HT _{2A} - binding	Comp. No.	5HT ₂ - binding	5HT _{2A} - binding	
	1	8.41	7.88		27	8.55	-
	2	7.44	-		28	8.91	8.12
20	4	7.9	-		30	8.79	8.08
	5	-	8.51		32	9.4	8.35
	6	9	8.19		33	8.35	-
25	7	8.12	7.64		35	8.43	-
	8	8.37	8.01		36	-	6.5
	9	8.02	7.24		37	8.49	7.35
30	10	7.59	6.34		38	8.09	7.9
	11	-	6.24		39	8.58	8.3
	12	-	6.21		41	7.84	-
	13	-	5.83		52	7.54	7.31
	14	-	6.38		53	7.75	7.63

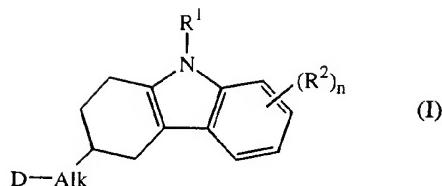
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40	Comp. No.	5HT ₂ - binding	5HT _{2A} - binding	Comp. No.	5HT ₂ - binding	5HT _{2A} - binding	
	15	-	5		67	8.74	8.36
	16	-	6.9		68	-	8.18
45	17	-	6.6		69	7.95	-
	18	-	5.6		86	-	8.34
	20	-	6.5		89	-	8.16
	21	-	7		90	-	8.21
50	22	-	6.2		95	8.13	7.24
	23	9	8.63		96	-	7.32
	24	8.71	8.07		113	8.3	-
	25	-	8.48		121	6.26	-
55	26	-	8.21		129	5.85	-

Claims

1. A compound of formula

5



10

a *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

15 R¹ is hydrogen, C₁₋₆alkyl, aryl or C₁₋₆alkyl substituted with aryl;

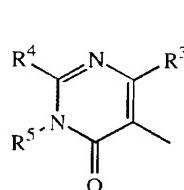
R² is each independently a halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy or nitro;

n is 0, 1, 2 or 3;

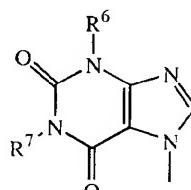
Alk is C₁₋₆alkanediyl;

D is 1- or 2-benzimidazolyl, 2(3*H*)benzoxazolone-3-yl or a radical of formula

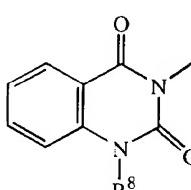
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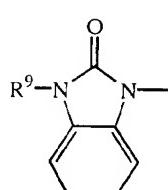
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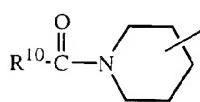
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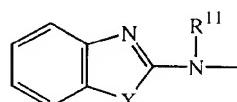
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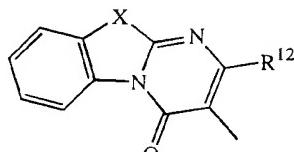
(d)



(e)



(f)



(g)

25

30

35

wherein

40 each X independently represents O, S or NR¹³;

R³ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

R⁴ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, mono- or di(C₁₋₆alkyl)amino or mono- or di(arylC₁₋₆alkyl)amino;

R⁵, R⁶, R⁷, R⁹, R¹¹, R¹² and R¹³ each independently are hydrogen or C₁₋₆alkyl;

45 R⁸ and R¹⁰ each independently are hydrogen, C₁₋₆alkyl or aryl; or

R⁴ and R⁵ taken together may form a bivalent radical -R⁴-R⁵- of formula

45

-CH₂-CH₂-CH₂- (a-1);

50

-CH₂-CH₂-CH₂-CH₂- (a-2);

55

-CH=CH-CH₂- (a-3);

-CH₂-CH=CH- (a-4) or

-CH=CH-CH=CH- (a-5);

wherein one or two hydrogen atoms of said radicals (a-1) to (a-5) each independently may be replaced

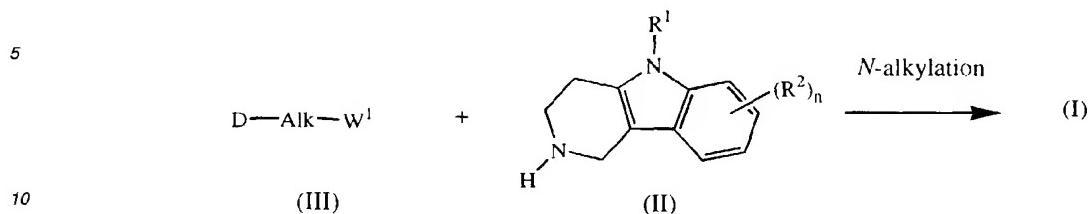
by halogen, C₁₋₆alkyl, arylC₁₋₆alkyl, trifluoromethyl, amino, hydroxy, C₁₋₆alkyloxy or C₁₋₁₀alkylcarbonyloxy; or where possible, two geminal hydrogen atoms may be replaced by C₁₋₆alkylidene or arylC₁₋₆alkylidene; or -R⁴-R⁵- may also be

5	-S-CH ₂ -CH ₂ -	(a-6);
	-S-CH ₂ -CH ₂ -CH ₂ -	(a-7);
	-S-CH=CH-	(a-8);
10	-NH-CH ₂ -CH ₂ -	(a-9);
	-NH-CH ₂ -CH ₂ -CH ₂ -	(a-10);
15	-NH-CH=CH-	(a-11);
	-NH-CH=N-	(a-12);
20	-S-CH=N-	(a-13) or
	-CH=CH-O-	(a-14);

wherein one or where possible two or three hydrogen atoms in said radicals (a-6) to (a-14) each independently may be replaced by C₁₋₆alkyl or aryl; and
25 aryl is phenyl or phenyl substituted with a halogen or C₁₋₆alkyl.

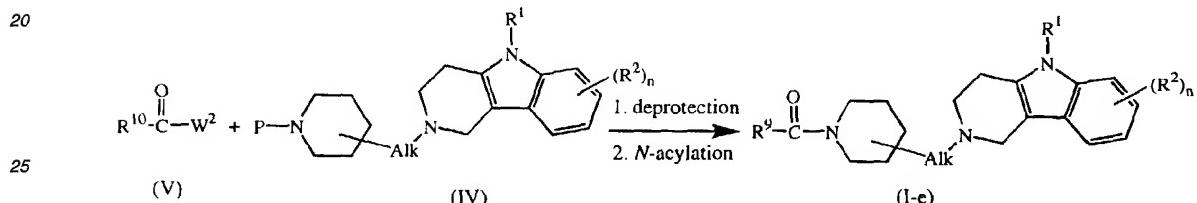
2. A compound according to claim 1 wherein n is 0 or 1 and R² is positioned in the 6-, 7- or 8-position of the γ -carbo-line moiety.
- 30 3. A compound according to claims 1 or 2 wherein R² is halogen, hydroxy, C₁₋₆alkyl or C₁₋₆alkyloxy; n is 0 or 1, Alk is C₁₋₄alkanediyl; D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ is amino; or -R⁴-R⁵- is a radical of formula (a-2) or (a-5) wherein one or two hydrogen atoms each independently may be replaced by halogen, C₁₋₆alkyl, trifluoromethyl or C₁₋₆alkyloxy, or -R⁴-R⁵- is a radical of formula (a-6), (a-7), (a-8), (a-11), (a-13) or (a-14) wherein one or where possible two hydrogen atoms each independently may be replaced by C₁₋₆alkyl; or D is a radical of formula (d) (f) wherein X is S or NR¹³ and R¹¹ is hydrogen; or a radical of formula (g) wherein X is S or NR¹³.
4. A compound according to claims 1 or 2 wherein R¹ is hydrogen; n is 0 or n is 1 whereby R² is a halogen, C₁₋₆alkyl, or C₁₋₆alkoxy; Alk is 1,2-ethanediyl and D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ is amino; R⁵ is C₁₋₆alkyl; or -R⁴-R⁵-is a radical of formula (a-2), (a-5), (a-6), (a-7), (a-8) or (a-11) wherein one hydrogen atom may be replaced by C₁₋₆alkyl; or D is a radical of formula (g) wherein X is NR¹³ and R¹² is C₁₋₆alkyl.
- 45 5. A compound according to claims 1 or 2 wherein R¹ is hydrogen; n is 0 or n is 1 whereby R² is a halogen or C₁₋₆alkyl, Alk is 1,2-ethanediyl and D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ and R⁵ are taken together to form -R⁴-R⁵- of formula (a-2), (a-5), (a-6), (a-7) or (a-8) wherein one hydrogen atom may be replaced by C₁₋₆alkyl.
6. A compound according to any one of claims 1 to 5 for use as a medicine.
7. The use of a compound as claimed in any one of claims 1 to 5 in the manufacture of a medicament for treating serotonin related disorders.
- 50 8. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.
- 55 9. A process for preparing a composition according to claim 8 by combining a compound as defined in any one of claims 1 to 5 as the active ingredient in intimate admixture with a pharmaceutically acceptable carrier.
10. A process for preparing a compound according to claim 1, characterized by,

a) *N*-alkylating a 1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole derivative of formula (II) with an alkylating reagent of formula (III)



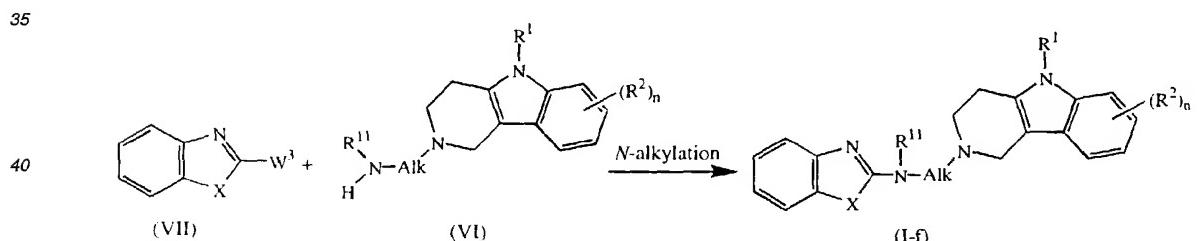
wherein W¹ represents an appropriate reactive leaving group and D, Alk, n, R¹ and R² are as defined in claim 1, in a reaction-inert solvent and in the presence of a suitable base and optionally in the presence of a catalyst;

b) deprotecting a *N*-protected intermediate of formula (IV) wherein P is a protective group and Alk, n, R¹ and R² are as defined in claim 1, and subsequently, *N*-acylating the resulting intermediate with an acyl derivative of formula (V) wherein W² is an appropriate reactive leaving group and R¹⁰ is as defined in claim 1, in a reaction-inert solvent and in the presence of a suitable base,



thus forming a compound of formula (I-e):

c) *N*-alkylating an amine of formula (VI) wherein Alk, n, R¹, R² and R¹¹ are as defined in claim 1, with an intermediate of formula (VII) wherein W³ is an appropriate reactive leaving group and X is as defined in claim 1, in a reaction-inert solvent and in the presence of a suitable base; or, *N*-alkylating an intermediate of formula (VI) with an intermediate of formula (VII) in the presence of copper;



thus forming an intermediate of formula (I-f):

d) and if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms or *N*-oxides thereof.



European Patent
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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 97 20 2761
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	EP 0 705 832 A (LILLY INDUSTRIES LTD) * the whole document *	1,2,6-10	C07D471/04 A61K31/435 C07D519/00
Y	US 4 798 896 A (ABOU-GHARBIA MAGID A ET AL) * the whole document *	1,6-10	
Y,D	GB 2 180 535 A (AMERICAN HOME PRODUCTS CORPORATION) * the whole document *	1,6-10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			C07D
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	16 January 1998	Henry, J	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	



European Patent
Office

INCOMPLETE SEARCH
SHEET C

Application Number

EP 97 20 2761

Claim(s) searched completely:
2-10

Claim(s) searched incompletely:
1

Reason for the limitation of the search (non-patentable invention(s)):

Obscurity of the formula in claim 1

Further reason for the limitation of the search:

Claim(s) searched completely:
2-10

Claim(s) searched incompletely:
1

Reason for the limitation of the search:

Formula(I) in claim 1 and page 1 of the description represents carbazole derivatives. Apparently all compounds prepared are tetrahydro gamma-carbolines derivatives. The search has been made for the compounds of the examples, namely for compounds with a cyclic nitrogen atom linked to the "alk-D" radical